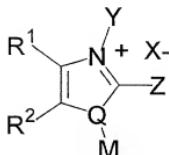


What is claimed:

1. A method of decreasing intraocular pressure or improving ocular accommodation in an animal, including a human, comprising administering an intraocular pressure decreasing or accommodation improving amount of (A) a compound of the formula I:
- 5



(I)

wherein

- a. R¹ and R² are

- 10 1. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C₁-C₃)alkylenedioxy, allyl, amino, ω -alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, 4-[C₆ or C₁₀]arylpiriperidin-1-yl, 4-[C₆ or C₁₀]arylpiperazin-1-yl, Ar {wherein, consistent with the rules of aromaticity, Ar is C₆ or C₁₀ aryl or a 5- or 6-membered heteroaryl ring, wherein 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be fused to a benzene, pyridine, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)}, Ar-alkyl, Ar-O, ArSO₂-, ArSO-, ArS-, ArSO₂NH-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-, or together R¹ and R² comprise methylenedioxy; or
- 15 2. together with their ring carbons form a C₆- or C₁₀- aromatic fused ring system; or
- 20
- 25

3. together with their ring carbons form a C₅-C₇ fused cycloalkyl ring having up to two double bonds including any fused double bond of the -olum or -onium containing ring, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxy carbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo substituents; or

4. together with their ring carbons form a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring may be optionally substituted with one or more 1-pyrrolidinyl-, 4-[C₆ or C₁₀]arylpiperazin-1-yl, 4-[C₆ or C₁₀]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C₁-C₃)alkylenedioxy groups; or

5. together with their ring carbons form a five to eight membered heterocycle, wherein the heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, and S(O)_n, where n=0,1, or 2;

b. Z is

1. hydrogen, alkyl, Ar—CH₂;

2. a group of the formula -NR³R⁴, wherein R³ and R⁴ may be independently hydrogen, alkyl, Ar, or Ar—alkyl-;

3. a group of the formula -CH(OR¹¹)R¹², wherein R¹¹ is hydrogen, methyl, ethyl or CH₃C(O)-; and R¹² is [C₁ to C₆]alkyl, Ar, or CO₂R¹³ wherein R¹³ is hydrogen methyl or ethyl;

4. a group of the formula -C(CO₂R¹³)(OR¹¹)R¹²

5. a group of the formula -CH₂WAr, wherein W is -(C=O)- or -S(O)_n- where n=1 or 2; or

6. a group of the formula -CH₂C≡C-R¹⁴, wherein R¹⁴ is (C₁-C₆)alkyl;

c. Y is

1. amino, or

2. a group of the formula -CH(R⁵)-R⁶ wherein

(a) R⁵ is hydrogen, alkyl-, cycloalkyl-, alkenyl-, alkynyl-, aminoalkyl-, dialkylaminoalkyl-, (N-[C₆ or C₁₀]aryl)(N-alkyl)aminoalkyl-, piperidin-1-ylalkyl-, 1-pyrrolidinylalkyl, azetidinylalkyl, 4-alkylpiperazin-1-ylalkyl, 4-alkylpiperidin-1-ylalkyl, 4-[C₆ or C₁₀]arylpiperazin-1-ylalkyl, 4-[C₆ or

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C_{10}]arylpiperidin-1-ylalkyl, azetidin-1-ylalkyl, morpholin-4-ylalkyl, thiomorpholin-4-ylalkyl, piperidin-1-ylalkyl, [C_6 or C_{10}]aryl, or independently the same as R^6 ;

(b) R^6 is

5 (1) hydrogen, alkyl (which can be substituted by alkoxy carbonyl), alkenyl, alkynyl, cyano- or R_s , wherein R_s is a C_6 or C_{10} aryl or a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

10 (2) a group of the formula $-W-R^7$, wherein R^7 is alkyl, alkoxy, hydroxy or R_s , wherein W is $-C(=O)-$ or $-S(O)_n-$ where $n=1$ or 2,

15 (3) a group of the formula $-W-OR^8$ wherein R^8 is hydrogen or alkyl,

20 (4) a group of the formula $-CH(OH)R_s$; or

25 (5) a group of the formula $-W-N(R^9)R^{10}$, wherein

30 [a] R^9 is hydrogen and R^{10} is an alkyl or cycloalkyl, optionally substituted by

 (i) [C_6 or C_{10}]aryl, or

 (ii) a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, said heteroaryl ring can be optionally substituted with one or more 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, and morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C_1-C_3)alkylenedioxy groups, or fused to a substituted phenyl or pyridine ring, wherein the ring fusion is at a carbon-carbon double bond of the heteroaryl ring, or

 (iii) a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

 [b] R^9 is hydrogen or lower alkyl and R^{10} is Ar; or

 [c] R^9 is hydrogen or lower alkyl, and R^{10} is a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, said heterocycle; or

[d] R⁹ and R¹⁰ are both alkyl groups; or

[e] R⁹ and R¹⁰ together with N form a heterocycle containing 4-10 ring atoms which can incorporate up to one additional heteroatom selected from the group of N, O or S in the ring, wherein the heterocycle is optionally substituted with (C₆-or C₁₀)aryl, (C₆-or C₁₀)aryalkyl, or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each such heteroaryl can be optionally

10 substituted with one or more 1-pyrrolidinyl, 4-[C₆ or C₁₀]arylpiperazin-1-yl, 4-[C₆ or C₁₀]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C₁-C₃)alkylenedioxy; or

[f] R⁹ and R¹⁰ are both hydrogen; or

15 d. Q is N, O or S;
 e. M is absent when Q is O or S;
 f. M is alkyl, vinyl or allyl, or independently the same as Y; and
 g. X is a pharmaceutically acceptable anion, or
(B) a pharmaceutically acceptable salt of the compound,
 20 wherein aryl or Ar can be substituted with, in addition to any substitutions specifically noted, one or more substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C₁-C₃)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω -alkylenesulfonic acid, alkylthio, allyl, amino, ArC(O)-,
 25 ArC(O)NH-, ArO-, Ar-, Ar-alkyl, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, 1-pyrrolidinyl, 4-[C₆ or C₁₀]arylpiperazin-1-yl-, 4-[C₆ or C₁₀]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl; and
 30 wherein heterocycles, except those of Ar, can be substituted with, in addition to any substitutions specifically noted, acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio,

amino, ArC(O)-, ArO-, Ar-, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl.

2. The method of claim 1, comprising administering an intraocular pressure

5 decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula -CH(R⁵)R⁶.

3. The method of claim 2, comprising administering an intraocular pressure

decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula -CH(R⁵)-W-R⁷.

4. The method of claim 2, comprising administering an intraocular pressure

decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula -CH(R⁵)-W-Rs.

15

5. The method of Claim 1, comprising administering an intraocular pressure

decreasing or accommodation improving amount of a compound of formula I, wherein R¹ and R² together with their ring carbons form a C₆- or C₁₀- aromatic fused ring which can be substituted by one or more halo, amino, alkyl, sulfonic acid, alkylsulfonyl or α -

20 alkylenesulfonic acid groups, or a C₁-C₃ alkylenedioxy group with the proviso that when Q is nitrogen R¹ and R² do not form a C₆ fused aromatic ring.

6. The method of Claim 1, comprising administering an intraocular pressure

decreasing amount of a compound of the compound of formula I, wherein Q is S, and Y

25 and Z are both -NH₂.

7. The method of Claim 1, further comprising administering an effective amount of a cholinergic agent.

30 8. The method of Claim 1, comprising administering an intraocular pressure

decreasing or accommodation improving amount of a compound of formula I, wherein
a. R¹ and R² are

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1. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxy carbonylalkyl, alkyl, (C_1-C_3)alkylenedioxy, allyl, ω -alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, halo, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, Ar {wherein, consistent with the rules of aromaticity, Ar is C_6 or C_{10} aryl or a 5- or 6-membered heteroaryl ring, wherein 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be fused to a benzene, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)}, Ar-alkyl, Ar-O, ArSO₂-, ArSO-, ArS-, ArSO₂NH-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-; or
2. together with their ring carbons form a C_6 - or C_{10} - aromatic fused ring system; or
3. together with their ring carbons form a C_5-C_7 fused cycloalkyl ring having up to two double bonds including any fused double bond of the -olum or -onium containing ring, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, aminocarbonyl, carboxy, fluoro, or oxo substituents; or
4. together with their ring carbons form a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring may be optionally substituted with one or more halo or (C_1-C_3)alkylenedioxy groups; or
5. together with their ring carbons form a five to eight membered heterocycle, wherein the heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, and S(O)_n, where n=0, 1, or 2;

b. Z is

1. hydrogen, alkyl, Ar—CH₂;
2. a group of the formula -NR³R⁴, wherein R³ and R⁴ may be independently hydrogen, alkyl, Ar, or Ar-alkyl-;

3. a group of the formula $-\text{CH}(\text{OR}^{11})\text{R}^{12}$, wherein R^{11} is hydrogen, methyl, ethyl or $\text{CH}_3\text{C}(\text{O})-$; and R^{12} is $[\text{C}_1 \text{ to } \text{C}_6]\text{alkyl}$, Ar, or CO_2R^{13} wherein R^{13} is hydrogen methyl or ethyl;

4. a group of the formula $-\text{C}(\text{CO}_2\text{R}^{13})(\text{OR}^{11})\text{R}^{12}$

5 5. a group of the formula $-\text{CH}_2\text{WAr}$, wherein W is $-(\text{C}=\text{O})-$ or $-\text{S}(\text{O})_n-$ where $n=1$ or 2; or

6. a group of the formula $-\text{CH}_2\text{C}\equiv\text{C}-\text{R}^{14}$, wherein R^{14} is $(\text{C}_1\text{--C}_6)\text{alkyl}$;

c. Y is

1. amino, or

10 2. a group of the formula $-\text{CH}(\text{R}^5)\text{R}^6$ wherein

(a) R^5 is hydrogen or alkyl;

(b) R^6 is

(1) hydrogen, alkyl (which can be substituted by alkoxy carbonyl), alkenyl, alkynyl, cyano- or Rs, wherein Rs is a C_6 or C_{10} aryl or a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

(2) a group of the formula $-\text{W--R}^7$, wherein R^7 is alkyl, alkoxy, hydroxy or Rs, wherein W is $-\text{C}(\text{O})-$ or $-\text{S}(\text{O})_n-$ where $n=1$ or 2;

(3) a group of the formula $-\text{W--OR}^8$ wherein R^8 is hydrogen or alkyl,

20 (4) a group of the formula $-\text{CH}(\text{OH})\text{Rs}$; or

(5) a group of the formula $-\text{W--N}(\text{R}^9)\text{R}^{10}$, wherein

[a] R^9 is hydrogen and R^{10} is an alkyl or cycloalkyl, optionally substituted by

(i) $[\text{C}_6$ or $\text{C}_{10}]\text{aryl}$, or

25 (ii) a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, said heteroaryl ring can be optionally substituted with one or more halo or $(\text{C}_1\text{--C}_3)\text{alkylenedioxy}$ groups, or fused to a substituted phenyl, or

(iii) a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

[b] R⁹ is hydrogen or lower alkyl and R¹⁰ is Ar; or

[c] R⁹ is hydrogen or lower alkyl, and R¹⁰ is a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms are selected from the group consisting of oxygen, nitrogen and sulfur, said heterocycle; or

[d] R⁹ and R¹⁰ are both alkyl groups; or

[e] R⁹ and R¹⁰ together with N form a heterocycle containing 4-10 ring atoms which can incorporate up to one additional heteroatom selected from the group of N, O or S in the ring, wherein the heterocycle is optionally substituted with (C₆-or C₁₀)aryl, (C₆-or C₁₀)aryalkyl, or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each such heteroaryl can be optionally substituted with one or more halo or (C₁-C₃)alkylenedioxy; or

[f] R⁹ and R¹⁰ are both hydrogen; or

d. Q is N, O or S;

e. M is absent when Q is O or S;

f. M is alkyl, vinyl or allyl, or independently the same as Y; and

g. X is a pharmaceutically acceptable anion, or

20 (B) a pharmaceutically acceptable salt of the compound,

wherein aryl or Ar can be substituted with, in addition to any substitutions specifically noted, one or more substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxy carbonyl,

alkoxycarbonylalkyl, alkyl, (C₁-C₃)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, or-

25 alkylenesulfonic acid, alkylthio, allyl, ArC(O)-, ArC(O)NH-, ArO-, Ar-, Ar-alkyl-, carboxy, carboxyalkyl, cycloalkyl, halo, trifluoromethyl, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid; and

wherein heterocycles, except those of Ar, can be substituted with, in addition to any substitutions specifically noted, acylamino, alkanoyl, alkoxy, alkoxy carbonyl, alkoxycarbonylalkyl, alkyl, alkylsulfonyl, alkylsulfinyl, alkylthio, ArC(O)-, ArO-, Ar-, carboxy, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl.

9. The method of claim 8, comprising administering an intraocular pressure decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula -CH(R⁵)R⁶.

5 10. The method of claim 9, comprising administering an intraocular pressure decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula -CH(R⁵)-W-R⁷.

11. The method of claim 9, comprising administering an intraocular pressure
10 decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula -CH(R⁵)-W-Rs.

12. The method of Claim 1, comprising administering an intraocular pressure
decreasing amount of a compound of the compound of formula I, wherein Q is S, Y and
15 Z are both -NH₂.

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